Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression

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Abstract: The present study employs a new framework to categorise the heterogeneous findings on the relationship between impaired reward processing and negative and affective symptoms of schizophrenia. Based on previous behavioural and neuroimaging studies we postulate that "wanting" (i.e. anticipation) of a reward is specifically related to apathy, whereas "liking" (i.e. hedonic impact) is related to anhedonia and depression–symptoms commonly observed in schizophrenia. Fifteen patients with schizophrenia or schizoaffective disorder treated with atypical antipsychotic drugs and fifteen healthy controls performed a probabilistic monetary incentive delay task while undergoing functional magnetic resonance imaging. At the group level we found no significant differences between patients and controls in neural activation during anticipation or receipt of a reward. However, in patients with schizophrenia specific relationships between ventral-striatal activation and symptoms were observed. Ventral-striatal activation during reward anticipation was negatively correlated with apathy, while activation during receipt of reward was negatively correlated with severity of depressive symptoms. These results suggest that the link between negative symptoms and reward anticipation might specifically relate to apathy, i.e. a lack of motivation and drive. Impaired hedonic reward processing might contribute to the development of depressive symptoms in patients with schizophrenia, but it is not directly associated with self-rated anhedonia. These results indicate the necessity of more specifically differentiating negative and affective symptoms in schizophrenia in order to understand the role of the reward system in their pathogenesis.

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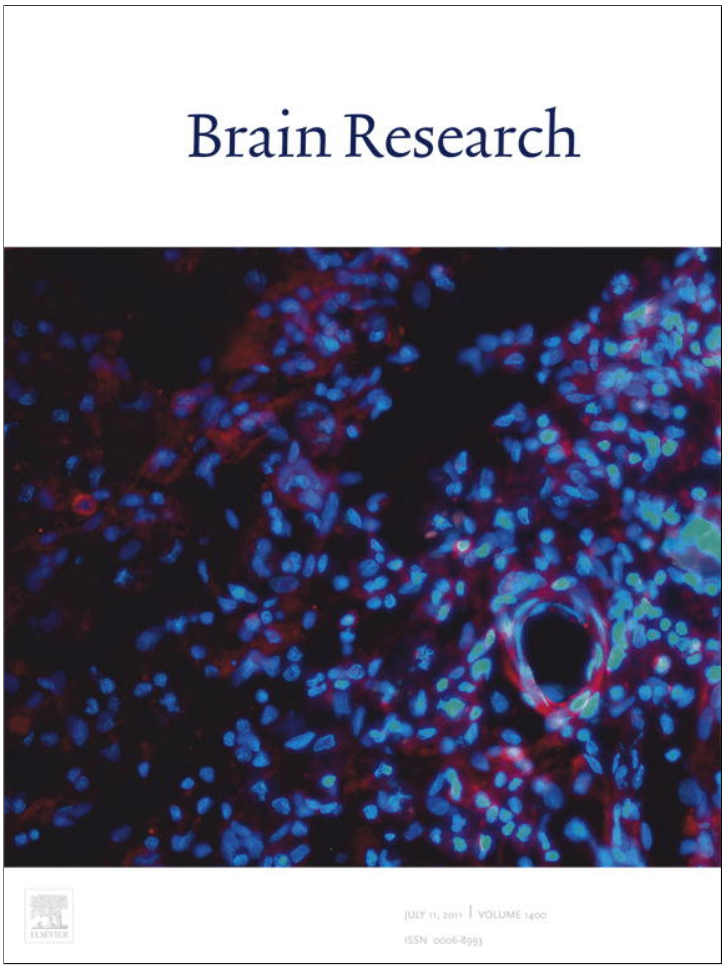

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Research Report

Neural correlates of evaluating hazards of high risk

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ABSTRACT

In personal and in society related context, people often evaluate the risk of environmental and technological hazards. Previous research addressing neuroscience of risk evaluation assessed particularly the direct personal risk of presented stimuli, which may have comprised for instance aspects of fear. Further, risk evaluation primarily was compared to tasks of other cognitive domains serving as control conditions, thus revealing general risk related brain activity, but not such specifically associated with estimating a higher level of risk. We here investigated the neural basis on which lay-persons individually evaluated the risk of different potential hazards for the society. Twenty healthy subjects underwent functional magnetic resonance imaging while evaluating the risk of fifty more or less risky conditions presented as written terms. Brain activations during the individual estimations of 'high' against 'low' risk, and of negative versus neutral and positive emotional valences were analyzed. Estimating hazards to be of high risk was associated with activation in medial thalamus, anterior insula, caudate nucleus, cingulate cortex and further prefrontal and temporo-occipital areas. These areas were not involved according to an analysis of the emotion ratings. In conclusion, we emphasize a contribution of the mentioned brain areas involved to signal high risk, here not primarily associated with the emotional valence of the risk items. These areas have earlier been reported to be associated with, beside emotional, viscerosensitive and implicit processing. This leads to assumptions of an intuitive contribution, or a "gut-feeling", not necessarily dependent of the subjective emotional valence, when estimating a high risk of environmental hazards.

1. Introduction

Analyzing the risk of environmental, personal and political hazards is an everyday challenge. A proper risk assessment is essential for survival by coping with respective threats and for allocating necessary resources. Many, if not most decisions are made with a certain grade of uncertainty resulting in a choice under risk. Then, risk can consist in a disadvantageous outcome

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Abbreviations: ACC, anterior cingulate cortex; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; IAT, implicit association task; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; TR, repetition time; VMPFC, ventromedial prefrontal cortex

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for the person in case of the "wrong" decision or in happiness after the right one. Or, risk may be represented by a concrete threat or incident which might occur or not. This has an emotional impact and such risk processing was associated with emotion processing (e.g. Bach et al., 2009; Mohr et al., 2010a). Thereby, particularly lay persons that are not familiar with for instance the scientific and statistical background of certain risky conditions are prone to a more affect- or emotion-based estimation when faced with the necessity of evaluating a risk or a benefit (Loewenstein et al., 2001; Slovic et al., 2002). They then rely stronger on previous experiences, trust, narratives or metaphors than on sound knowledge (Fischhoff et al., 1982; Sjöberg, 1998), and they may use somatic signals associated with the emotional impact (Damasio, 1996) related to a hazard as a cue for intuitively estimating the risks: "risk as feelings" (Slovic et al., 2004).

Recent studies provided a profound investigation and discussion on the relation of risk processing and emotions regarding the neurobiological backgrounds (Bach et al., 2009; Mohr et al., 2010a; Quartz, 2009; Vorhold et al., 2007; Xu et al., 2009). A meta-analysis assessing risk-processing related brain regions identified a network including bilateral anterior insula, dorsomedial and posterior thalamus, dorsomedial and right dorsolateral prefrontal cortex (DM/DLPFC), and right parietal cortex to be involved (Mohr et al., 2010a). In this context, it was argued that lay-persons may recruit more emotion-associated brain areas as insula, amygdala and thalamic regions during risk processing (Anderson et al., 2003; Craig, 2002; Critchley et al., 2004; Singer et al., 2009; Vorhold et al., 2007).

The studies in this field particularly aimed at elucidating the neurobiological basis of risk assessment by means of functional magnetic resonance imaging (fMRI) using conditions with a subject-related risk implemented in the experimental tasks. Presented stimuli or terms had to be assessed in relation to a personal risk for the subject, or decision making was investigated under risky conditions with reward or loss for the subject (overview in Mohr et al., 2010a, e.g. Bach et al., 2009; Christopoulos et al., 2009; Huettel, 2006; Preuschoff et al., 2006; Quartz, 2009; Smith et al., 2009; Vorhold et al., 2007; Xu et al., 2009, and others). This meant also a direct emotional impact of the risk-related stimulus to the subjects: a possibly immediate negative consequence as fear or enjoying a positive outcome. Further, related studies primarily investigated risk evaluation versus control conditions that did not contain a risk evaluation component. Such, activity associated with estimating specifically the grade of for instance a high level of risk was not investigated. Accordingly, it appears valuable to investigate a risk condition which does not focus on a direct personal risk but on general risk evaluation. Therefore, subjects can rate the risk of certain hazards for the society and not for themselves. Further, in order to focus on brain activity particularly associated with a higher degree of risk, conditions with a higher risk can be compared with those of lower risk. This appears more suitable to investigate activation associated with gradually increasing risk than comparing with a non-risk control condition.

Our aim was to use such a methodological approach in order to assess the neurobiological backgrounds of risk processing. Based on the mentioned previous reports associating risk and emotion processing circuits (Mohr et al., 2010a; Quartz, 2009) we hypothesized that evaluating the degree of risk for the society of various hazards will in case of high risk recruit brain areas involved in different aspects of emotion processing despite addressing no imminent personal meaning. In this context, experience-based emotional signals or markers may be important to contribute to risk estimation. Primary areas of interest were thus insula, thalamus, lateral and medial prefrontal regions and amygdala.

We used non-imminent and non-personal risk terms representing possible hazards for the society with the instruction to assess the risk for the general (Swiss) society in order to differentiate from a personal emotional relation as far as possible (Slovic et al., 2004). For instance, a condition as "skiing" might be associated with positive emotions for the individual, but might represent a certain risk for the society (or not) due to a high accident rate. Further, we focused on the evaluative aspect and less on the decision making or choice process by analyzing the evaluation period prior rating feedback. Our approach is in line with the risk perception literature, in which people's risk perception is similar measured as in our study, in order to find out why societies are concerned about some hazards, but not other hazards (Slovic, 1987). Thereby, the subjects did not have to decide for a certain action but to indicate their risk estimation of a presented term. In this context, and differing from previous studies contrasting general risk evaluation with non-risk control conditions, we analyzed brain activation specifically associated with high versus low risk. Further, we also discriminated activity in the earlier phases of risk evaluation in order to detect brain regions with a more phasic or initial contribution to the evaluation process. Finally, the results were exploratorily compared with individual emotion ratings of the same hazards.

2. Results

2.1. *Behavioral data*

Twenty subjects were scanned of which 18 subjects were included into the analysis. Altogether, 890 trials were presented and rated (out of 900 trials = 50 trials per subject, 10 trials were not presented in one subject due to technical reasons). The subjects attributed low risk to on average 16.9 terms (SD 7.2), medium risk to 18.8 terms (SD 6.8) and high risk to 13.7 terms (SD 7.1), resulting in overall n = 305 trials with low risk, medium risk in n = 338 trials and high risk in n = 247 trials. The correlation of the individual risk and emotion ratings revealed in 8 of 50 terms a significant correlation. In 42 terms we found no correlation between individual rating of emotional valence and rating of the risk for the society. The mean rating data for risk and emotional valence are presented in the Supplementary Table S1.

2.2. *fMRI results*

Comparing the conditions 'high risk'- and 'low risk'-evaluation for the whole presentation period of 5940 ms with a random effects analysis, we found a stronger activation in the 'high risk' condition in left anterior insula, medial thalamus, left head of the caudate nucleus, the posterior cingulate cortex (PCC) and the precuneus (Fig. 2, Table 1).

Table 1 – High risk versus low risk in the whole evaluation period.

	Peak X	Peak Y	Peak Z	Cluster size mm^3	t-max
Ant. insula L (Fig. 3A)	36	17	−5	116	4.6
Med. thalamus	3	−7	−2	172	4.7
Posterior cingulate cortex L	−6	−34	28	403	5.0
Caudate L (Fig. 3B)	−6	11	10	264	4.5
Precuneus	−6	−73	31	122	4.7

Contrast 'high risk versus low risk' during the complete period of risk evaluation (random effects analysis $p<0.001$). Abbreviations: ant anterior, L left, med medial.

Table 2 – High risk versus low risk in deconvolution analyses of divided evaluation period.

	Peak X	Peak Y	Peak Z	Cluster size mm3	t-max
a.) First volume					
Med. thalamus R	12	−7	−2	157	3.0
Med. thalamus L	−9	−10	1	227	3.2
Temporo-occipital cortex R	45	−67	16	928	3.3
Temporo-occipital cortex L	−42	−70	19	1503	3.6
Precuneus L	−9	−70	34	415	3.4
Inferior temporal gyrus L	−54	−40	−12	256	3.5
b.) First two volumes					
Ant. insula R (Fig. 2A)	36	14	−8	355	4.3
Med./ant. thalamus blt (Fig. 2B)	−6	−7	1	1631	4.2
Head of caudate nucleus L	−12	11	13	244	3.9
Precallosal cingulate cortex (Fig. 2C)	6	32	16	268	3.6
Ant. cingulate cortex L	−9	23	28	142	3.7
Dorsolateral PFC L (Fig. 2D)	−33	−1	49	1712	4.2
Dorsolateral PFC R	45	−4	43	287	3.9
Med. PFC L	−6	2	58	685	3.8
Posterior cingulate cortex	0	−40	28	546	3.6
Temporo-occipital cortex L (Fig. 2E)	−39	−70	22	2235	4.2
Temporo-occipital cortex R	45	−70	25	981	4.1
Precuneus L	−9	−70	34	1527	4.7
Inferior temporal gyrus L	−51	−37	−15	306	4.3

Activated regions during a.) the first ($p<0.005$) and b.) the first two volumes ($p<0.001$) of the evaluation and presentation period, comparing 'high risk versus low risk' by applying a deconvolution analysis. Abbreviations: R right, L left, blt bilateral, Med medial, inf inferior, ant anterior, cap caput, ncl nucleus, caud caudatus, ACC anterior cingulate cortex, PFC prefrontal cortex.

In the deconvolution analysis, the early phase of the evaluating period during the first volume revealed activation in bilateral medial thalamus and in posterior higher perception processing regions such as bilateral temporo-occipital junction and precuneus on an exploratory significance level of $p<0.005$. When considering the first two volumes together, we found additional activation on a level $p<0.001$ in the anterior cingulate cortex (ACC), right anterior insula, caudate nuclei, medial prefrontal cortex (MPFC) and right dorsolateral prefrontal cortex (DLPFC; Fig. 3, Table 2). Results of the medium risk terms were assessed exploratorily and are provided descriptively with the time courses in the figures, showing a signal change ranging between the activations associated with low and high risk evaluation.

When comparing the activations associated with those terms individually rated to be of negative versus positive, or negative versus neutral emotional valence, we observed no stronger activation related to the negative valence on the level $p<0.001$ (random effects). Particularly, we found no activity related to negative affect in those regions identified to be associated with high risk also on an exploratory level of $p<0.01$ (random effects).

3. Discussion

Our aim was to investigate neural correlates associated with estimating a high risk of environmental and technological hazards for the society. We found distinct brain regions involved, comprising prefrontal, insular, and posterior cortical regions, as well as medial thalamus and caudate head. These results are discussed in the context of emotional and intuitive processing.

3.1. *Anatomical and functional features of the brain regions involved in risk-evaluation*

Estimating distinct hazards to be of high risk was associated with medial thalamic and anterior insular activation. Anatomically, medial thalamic regions receive input from viscerosensitive and pain mediating brainstem areas such as the parabrachial nucleus, the subnucleus reticularis, and the periaqueductal gray (Craig, 2002; Vogt, 2005). They are considered to form a relay within the viscerosensitive pathway towards particularly insular regions, ACC and amygdala (Augustine, 1996; Craig, 2002; Vogt, 2005). The insula is involved in the processing of multimodal visceral, sensory and emotional stimuli (Calder, 2003; Craig, 2002; Critchley et al., 2004; Damasio et al., 2000; Paulus and Stein, 2006; Singer et al., 2009). Insular regions have a wide range of reciprocal connections to prefrontal areas, ACC, medial thalamus, amygdala, hypothalamus, and brainstem regions as the parabrachial nucleus for relaying visceral afferents (Augustine, 1996). It was proposed that the interoceptive sensation of bodily signals depends on input from the viscera represented in the anterior insula (Critchley et al., 2004; Singer et al., 2009). In the context of risk processing, thalamic and insular contributions were reported during intertemporal choices involving losses which were associated with accompanying negative emotions (Xu et al., 2009). Thalamus and insula were also found to be involved in risky decisions and in anticipating risk (Huettel, 2006; Mohr et al., 2010a, 2010b). We here propose medial thalamus and anterior insula to be involved in the mediation of bodily interoceptive signals for evaluation purposes in response to the faced hazard.

We also found left caudate head activation associated with high risk, particularly in the initial phase of the evaluation

period. The caudate head shares prominent connectivity with the DLPFC through a series of parallel loops that project from the cortex to the input and output nuclei of the basal ganglia, then to the ventral–anterior and dorso-medial nuclei of the thalamus, and then back to the cortex (Alexander et al., 1986; Middleton and Strick, 2002). The caudate, particularly its head, has been proposed to be sensitive to implicit executive processing (Melrose et al., 2007; Seger and Cincotta, 2005), and being involved in intuition and implicit learning (Lieberman, 2000). Functional imaging studies link activity in the head of the caudate with information integration (Seger and Cincotta, 2002) and with executive functions related to probabilistic classification (Poldrack et al., 1999). A recent study reported the caudate nucleus to be involved in a task assessing risk-averse attitudes (Engelmann and Tamir, 2009). Taken together, the caudate in the context of risk estimation may function as a relay between cortical evaluation and thalamic signaling contributing to classification of the presented terms and to selection of implicit behavioral coping strategies.

The ACC, also activated during the 'high-risk' condition, is involved in conflict monitoring with potential affective consequences comparing the actual state with a desired state (Carter et al., 2000; Vogt, 2005). Being confronted with a high risk condition means a discrepancy to the desired state, resulting in a conflict signal. Cingulate regions are known to mediate integration and evaluation of emotional, motivational and cognitive information, and to modulate attention (Bishop et al., 2004; Vogt, 2005) with direct connections to amygdala, thalamus, prefrontal and insular areas and to the posterior parietal lobe (Goldman-Rakic, 1988). Cingulate activity in risk tasks was associated with a higher probability of a risky choice (Christopoulos et al., 2009) and was increased when risky choices involved immediate losses (Xu et al., 2009). Activation within the PCC was suggested to signal the subjective preferences that guide visual orienting within a gambling task comprising risky choices (McCoy and Platt, 2005). ACC and PCC were reported to be involved throughout all phases of risky decision making in a task concerning financial aspects (Engelmann and Tamir, 2009; Shackman et al., 2011).

We also found activation in medial and dorsolateral PFC when estimating high risk. This indicates an association with internal control and executive functions (Miller and Cohen, 2001; Wood and Grafman, 2003) which are regularly present in studies assessing cognitive and emotional functions (Pessoa, 2008). The contribution of these areas lead to argue that components of an analytical system are also involved in risk processing in lay people, or that executive strategies may be primed or selected for instance in the DLPFC (Mohr et al., 2010a). This can be accounted also to the specific instruction to rate the hazards regarding the risk for the society which may favor analytic processes apart emotional or intuitive components.

Posterior cortical activations associated with high risk occurred in temporo-occipital cortex regions and in the precuneus. The temporo-occipital junctional cortex, covering sensory associative cortices, is involved in multisensory integration of information (Beauchamp, 2005), which is increased by attention-requiring processes and efforts of performance (Mesulam, 1998), and in theory of mind (Lee and Siegle, 2009). The activation in the current study, found already in the very early evaluation period, may indicate an attentional bias towards risk-related terms, which also has been shown in the context of anxiety (Lee and Telch, 2008). The precuneus was reported to be involved in episodic memory retrieval and self-related processing (Cavanna and Trimble, 2006), which are also relevant during risk estimation.

Regarding the explorative deconvolution analysis and descriptively the time courses, we found anterior insula, medial thalamus and anterior cingulate to be active in the earlier periods of risk evaluation. This implies a role of a quicker and more phasic signaling in the context of detecting or estimating a high risk.

Taking together the brain activations and their functional implications, one might suggest pathways of risk processing. These include temporo-occipital areas for initial stimulus analysis with respect to the impact for the subject and others. They further comprise an intuitive estimation involving viscerosensitive areas as medial thalamus and insula, with a supposed bottom-up link towards prefrontal areas via the caudate for possibly selecting implicit strategies. This finally leads to evaluation and decision making involving prefrontal areas, based on a nominal value comparison regarding the impact for the person involving cingulate regions.

3.2. *Intuitive risk estimation and "gut"-feelings*

Risk evaluation by lay persons has been considered to be based on emotional signals, expressed as "risk as feelings" (Loewenstein et al., 2001; Slovic et al., 2004), and to involve an affect-based experiential rather than an analytical system (Slovic et al., 2004; Vorhold et al., 2007). For instance, implicit measures may reveal negative attitudes towards for instance nuclear power that were not detected by explicit measures (Siegrist et al., 2006). The experiential system may be more important than the analytic system when lay people assess technological risks compared to technical experts.

Our data enhance and differentiate this view by supporting the contribution of a viscerosensitive component to the estimation of high risk. Earlier reports addressing risk evaluation emphasized the emotional components as reflected by for instance amygdala, ventromedial prefrontal cortex (VMPFC), and insular activation (Fukui et al., 2005; Huettel, 2006; Mohr et al., 2010a; Quartz, 2009; Vorhold et al., 2007; Weller et al., 2007; Xu et al., 2009). These regions may be involved in risk evaluation in general, independent of the degree of risk. This may explain on the one hand that these regions were not found to be differentially activated here when contrasting high versus low risk, and on the other hand the finding of areas specifically associated with high risk that were not identified in previous studies.

A discriminative view of emotional and evaluative aspects of risk assessment is supported by our finding that the majority of our terms, 42 out of 50, had no correlation between risk estimation and emotional valence. Further, analyzing the functional data based on the individually rated emotional valence of the potential hazards did not show any brain regions to be activated. This has, of course, to be regarded as exploratorily, also because the emotional arousal contributing to emotion related brain activation was not directly assessed, but it at least implies that risk evaluation and emotional evaluation may not be coupled tightly.

Within this context, we revealed a contribution of areas representing associations with implicit and viscerosensitive functions as caudate, medial thalamus and insula. This lends support to the assumption of an evaluation concerning the risk of hazards by lay-persons based on intuitive processes and bodily signals. These are linked to emotions and may support affective processing, however, they may form an own functional entity.

Regarding proposed systems for decision making in the context of risk analysis, the analytical and the experiential system (Slovic et al., 2004), viscerosensitive signals are suggested to serve the experiential one. This is used when lay persons have to base their decision more on experiences, which are biased more by emotional influences, than on logical and analytical considerations or on scientific facts (Finucane et al., 2000). From a phylogenetic perspective, an evaluation system based on experiences and non-analytical estimations makes sense and is important in beings without highest rational capacities, and for quick response in case of danger. In human, these evaluation systems are accordingly used in conditions without sufficient knowledge for analytical approaches, thus when intuition is required (Lieberman, 2000; Volz and von Cramon, 2006). In such evaluation and decision contexts, we often rely on signals that are commonly termed as "gut"-feelings.

3.3. *Conclusion*

We emphasize a contribution of particularly insular, thalamic and caudate regions to be involved in signaling high risk, which here was not associated with the emotional valence of the risk items. These areas have earlier been reported to be associated with, beside emotional, viscerosensitive and implicit processing. This implies assumptions of an intuitive contribution, or a "gut-feeling", not necessarily dependent of the subjective emotional valence, when estimating a high risk of hazards for the society. In risk communication, this affective foundation, based on "gut"-feelings, of lay people's assessment of hazards may be taken in to account.

4. Experimental procedures

4.1. *Subjects*

Twenty healthy subjects (age 22–29 years, mean 25.1, all right handed, 11 females) were recruited to participate in this study and gave written informed consent. The study was approved by the local ethics committee. Two subjects were excluded afterwards because of movement artifacts (exceeding 3 mm in one direction), such that data of 18 subjects were analyzed. The subjects were healthy without any psychiatric or neurologic history and did not take any psychotropic medication.

4.2. *Experimental design*

During fMRI scanning, the subjects evaluated the general risk of different hazards such as "nuclear power", "smoking", "bicycling" etc. for the society (complete list originally in German, English translation in Supplementary material). A related paradigm has earlier been used for examining the research question of why lay people perceive different hazards differently (Siegrist et al., 2005; Slovic, 1987), and was adapted for the current study comprising common potential hazards. The subjects were presented written terms for 5940 ms (equivalent to 3 repetition times, TR, for the fMRI volumes). In this period, they were instructed to judge the risk of the respective hazard for the local, i.e. Swiss, society. So, this period comprised the processes of perceiving, evaluating and judging/estimating of the hazards ("evaluating period"). Subsequently, a five-step visual analog scale was presented for 3960 ms (two volumes) on which the subjects indicated the individually estimated risk from very low to very high by moving a cursor using a trackball with the right hand (Fig. 1), the "rating period". Altogether, 50 stimuli (terms) were presented in a randomized order. The following baseline period (13,700 ms, 7 TR) was of sufficient duration to allow the blood oxygen level-dependent signal to wear off before the next trial. The task was programmed with Presentation™, Neurobehavioral Systems, USA. The terms were presented in black letters on a white background via digital video goggles (Resonance Technologies, Northridge, CA) in a size approximately equivalent to font size 24 in the focus of a laptop screen in reading distance such that minimal eye movements were required to read the terms. After scanning, the subjects were asked to rate the subjective emotional valence of the risk terms on a nine-step visual analog scale (very negative = 1, neutral = 5, very positive = 9).

4.3. *Data acquisition*

Imaging was performed with a 3.0 T GE Signa™ HD Scanner (GE Medical Systems, Milwaukee). Echoplanar imaging was performed for fMRI (repetition time TR/echo time TE 1,980 ms/32 ms, 22 sequential axial slices, whole brain, slice thickness 3.5 mm, 1 mm gap, resulting voxel size 3.125 × 3.125 × 4.5 mm, matrix 64 × 64 pixels, field of view 200 mm, flip angle 70°). 611 volumes were obtained per subject, 12 per trial. Four initial volumes were discarded to allow for T2 equilibration effects, seven volumes were added for a final baseline. High-resolution 3-D T1 weighted anatomical volumes were acquired (TR/TE 9.9/2.9 ms; matrix size 256 × 256; 1 mm × 1 mm × 1 mm resolution) for coregistration with the functional data.

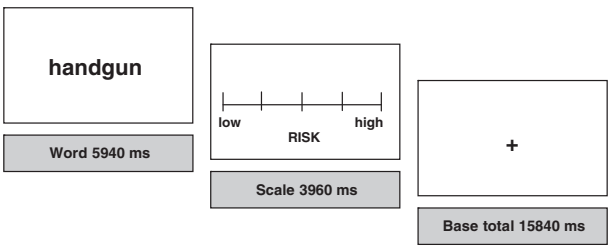

Fig. 1 – Experimental task. Trials started with a term presentation of near 6 s with the task to evaluate the risk of the term for the society. This was followed by a feedback period of near 4 s. A baseline condition of near 16 s was implemented between the trials.

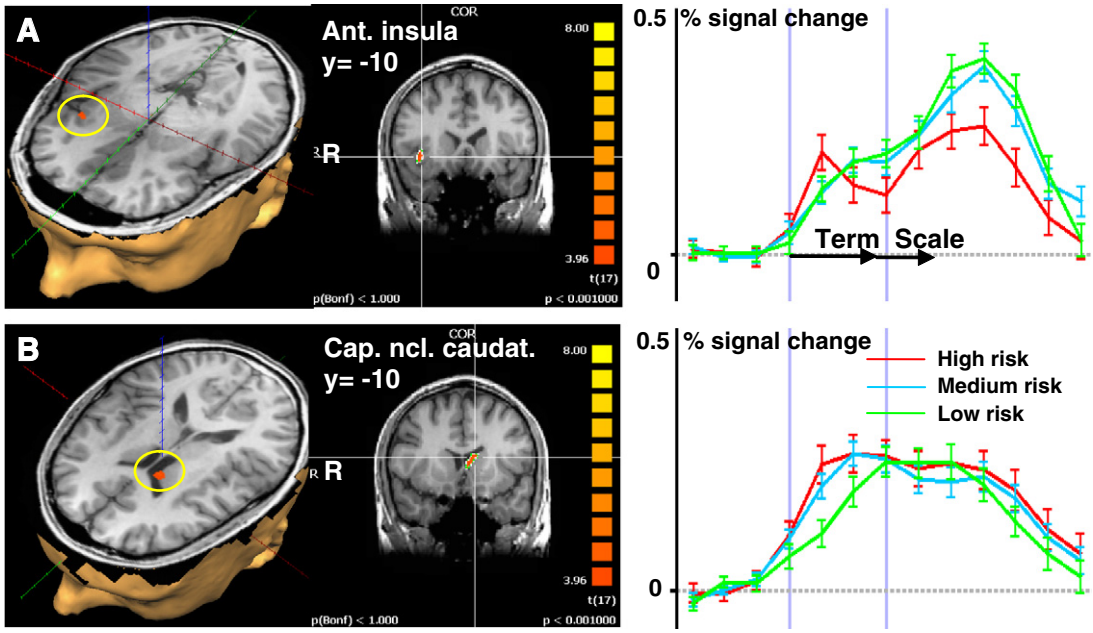

Fig. 2 – Brain activation with color coded maps and time courses according to a random effects analysis ($p<0.001$) of the whole evaluation period comparing high risk against low risk. A. insula, B. head of caudate.

4.4. *Data analysis*

fMRI data were analyzed using BrainVoyager™ QX 1.10.1 (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the functional scans included motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. The individual 3D data sets were transformed into Talairach space resulting in a voxel size of 3 mm × 3 mm × 3 mm and then spatially smoothed with an 8 mm Gaussian kernel for subsequent group analysis. From each included subject ($n=18$), the individual ratings of each term were analyzed concerning risk value and divided in three groups: low risk, medium risk, high risk. Low risk was defined as ratings between 1.00 and 2.00, medium risk between 2.01 and 3.40 and high risk between 3.41 and 5.00 based on the distribution of the evaluation ratings (consider Supplementary material Figure S2). Individual protocols for each subject for the fMRI-analysis were built comprising the individually rated items meeting the three conditions low, medium, high risk and the respective three presentation conditions of the rating scale as predictors resulting in each six predictors for the design matrix. The periods were modeled as epochs using a two-gamma hemodynamic response function provided by BrainVoyager™ adapted to the applied period duration.

The fMRI data analysis, based on the general linear model (GLM), comprised the following steps: First, fixed effects analyses were calculated separately for each subject for the contrast comparing the individual conditions 'high risk' versus 'low risk' resulting in summary images. The summary images were subjected to second level group analyses. Thus, those trials in which the terms were rated with 'high' and 'low' risk were considered, irrespective of the word contents. For analyzing the whole evaluation period, three-dimensional statistical parametric maps were calculated for the groups using a random effects analysis. The main analysis focused on the contrast "high risk>low risk". The voxel-wise threshold for reporting results in the random effects analysis was set at $p<0.001$. To correct for multiple comparisons, a Monte Carlo simulation was used (Goebel et al., 2006) for estimating cluster-level false-positive rates on these maps, yielding after 10.000 iterations a minimum cluster size threshold of 4 voxels of 3×3×3 mm (108 mm^3), corresponding to a corrected cluster level $p<0.04$.

As the evaluating period comprised early perceptual and rapid judgmental as well as later explicitly estimative and perhaps already preparatory processes we were further interested in brain activity particularly in the earlier periods of risk evaluation with an exploratory approach. When of course overlapping with the analysis covering the whole period, this analysis revealed regions particularly active in the initial phase of evaluation, of which the associated activation may be mitigated when analyzing the whole period. This appeared important for us, as risk evaluation may be regarded as a chain of process comprising initial perception of the stimulus, quick intuitive/emotional estimation, rational consideration and a final decision. Therefore, we applied a deconvolution analysis (Dale and Buckner, 1997; Pierce and Redcay, 2008) to achieve a better temporal resolution: we defined the three volumes acquired during the assessment period as single time points using no specific hemodynamic response function. We analyzed the brain activity within the period of the first volume separately (approximately 2 s), and also for the first two volumes (near 4 s) of the three volume period. For these analyses, we used a statistical threshold of $p<0.001$, corresponding to a correction for multiple comparisons according to the FDR

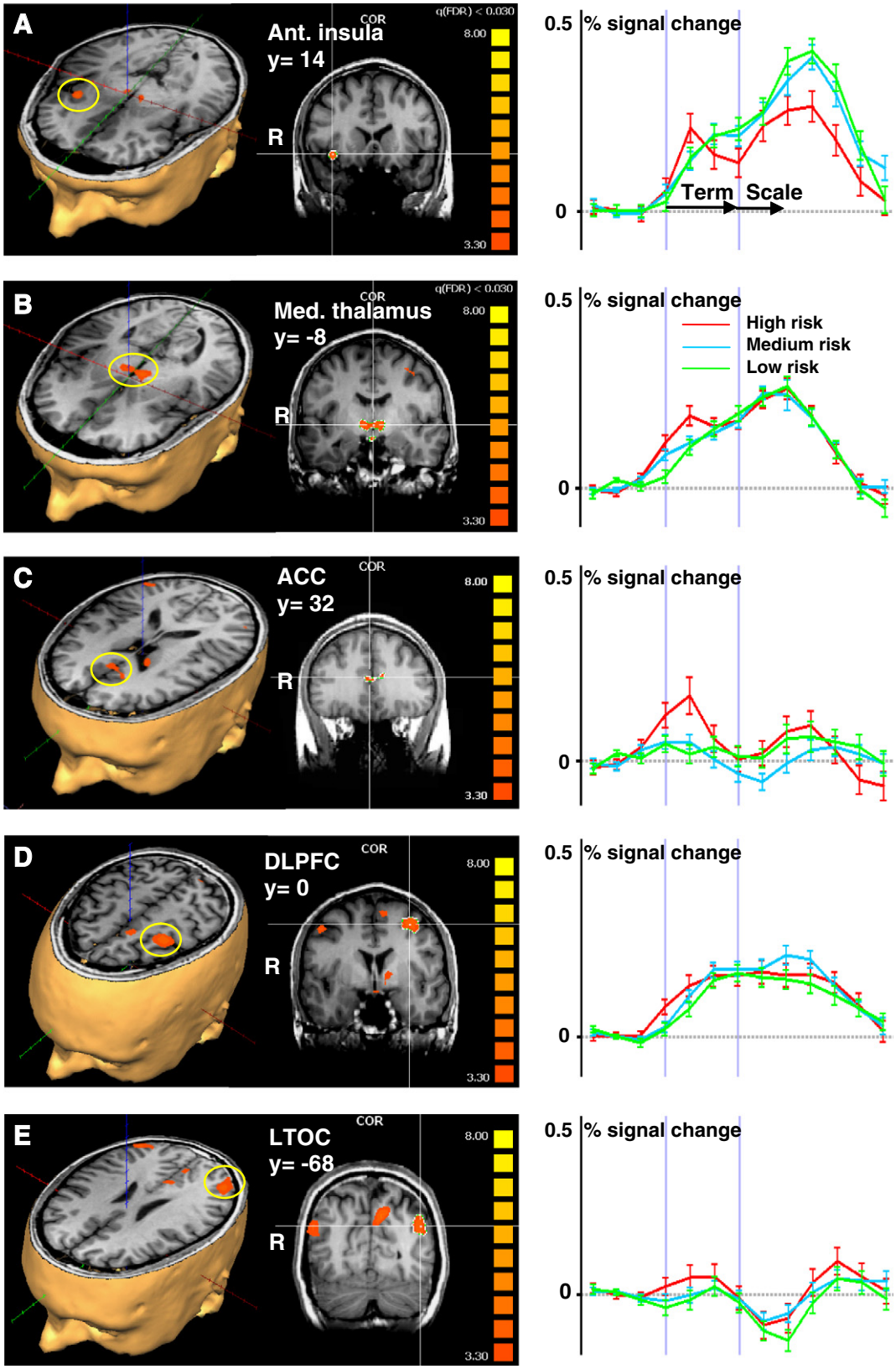

Fig. 3 – Brain activation including time courses according to the deconvolution analyses ($p < 0.001$) of the first 4 s of risk evaluation high vs. low risk, here A. anterior insula, B. medial thalamus regions, C. anterior cingulate cortex (ACC), D. dorsolateral prefrontal cortex (DLPFC), and E. lateral temporo-occipital cortex (LTOC).

corrected $p<0.05$, together with a cluster threshold of 108 mm^3, and also analyzed exploratorily with a threshold of $p<0.005$ (uncorrected). By using this approach, those areas were identified where the activation significantly differed between the conditions 'high risk' and 'low risk' during the period of the first volume and during the first two volumes together.

Based on the emotion ratings, we performed an analysis of brain activity during the presentation/evaluation period of those terms rated individually to be associated with negative affect compared with those rated positive or neutral. Analog to the risk analysis, the threshold was set to $p<0.001$ in a random effects analysis. Exploratorily, we assessed activity also at $p<0.01$. Finally, the emotion ratings were compared by using Pearson's correlation with the risk ratings during the experiment in the scanner.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.brainres.2011.05.023.

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